DECLARATION BY DR WILLARD M. FREEMAN

1. I, Dr. Willard M. Freeman, declare that the following statements are, to my knowledge, true as of the date of execution of this declaration.

2. I hold a BA in Chemistry and English from Wake Forest University and a PhD in Pharmacology from Wake Forest University School of Medicine. I am currently the Director of the Functional Genomics Core Facility at the Penn State University Milton S. Hershey Medical Center and an Assistant Professor in the Department of Pharmacology. I have expertise, in relevant part, in protein sequencing and analysis, gene sequencing and analysis, gene expression and regulation, polymerase chain reaction, reverse transcriptase polymerase chain reaction, plasmid engineering, clone production and screening, and functional genomics, proteomics and bioinformatics.

2. I was asked to provide my technical and professional expert opinion concerning whether there is support for the polypeptide sequence shown in SEQ ID NO:1 of European Patent No. EP 1 054 894 in US Provisional Patent Application Serial No. 60/073,763.

3. The primary question posed to me regarding my technical and professional expert opinion is whether or not the 655 amino acid sequence of breast cancer resistance protein (BCRP), depicted as SEQ ID NO:1 in European Patent No. EP 1 054 894, can directly and unambiguously be derived from US Provisional Patent Application Serial No. 60/073,763. In my technical and professional expert opinion, SEQ ID NO:1 in European Patent No. EP 1 054 894 can unequivocally be derived from US Provisional Patent Application Serial No. 60/073,763 for the reasons discussed below.

4. It is generally known to those that work in the field of molecular biology that when determining an open reading frame (ORF) a polynucleotide sequence is scanned for start and stop codons, which will elucidate a potential ORF. This can be done manually

or by using specialized software. In this case, potential ORFs were determined using the software program FRAMES and it was apparent that the start codon used to elucidate potential ORFs was ATG, which codes for the amino acid methionine (p. 21-22 of US Provisional Patent Application Serial No. 60/073,763 and Figure 2C). It was apparent that ATG was the start codon used because the ORF, stated at page 21 of the priority document, starts with an ATG. By using the ORF stated in the priority document I was able to easily and readily derive the protein sequence of SEQ ID NO:1 in European Patent No. EP 1 054 894 by simple and routine means. This was done by using multiple, standard software programs [ExPASy Translate Tool (http://expasy.org/tools/dna.html) and EMBOSS Transseq (http://www.ebi.ac.uk/Tools/emboss/transeq/)] in which I input the polynucleotide sequence of the ORF. The ORF was translated into its protein sequence, which was then compared to the protein sequence of SEQ ID NO:1 using a standard software program [EMBOSS Pairwise Alignment Algorithms (http://www.ebi.ac.uk/Tools/emboss/align/)] and was identical in all cases. The protein sequence corresponding to the ORF in US Provisional Patent Application Serial No. 60/073,763 is 100% identical to SEQ ID NO:1 in European Patent No. EP 1 054 894.

5. In regard to the deduced amino acid sequence for BCRP presented in the provisional patent application, it is noted that errors in amino acid sequences of deduced amino acid sequences routinely occur in the field of molecular biology. This is apparent by the plethora of annotations of amino acid sequences in databases such as GenBank. Sequence errors for deduced amino acid sequences can be a result of a myriad of factors with a prevalent error being human error (e.g., inputting of an incorrect sequence). In my opinion the protein sequence for BCRP in US Provisional Patent Application Serial No. 60/073,763 and Figure 2A is an obvious error. To begin with, I note that US Provisional Patent Application Serial No. 60/073,763 states that the ORF for BCRP corresponds to the amino acid sequence shown in Figure 2A. However, the amino acid sequence in Figure 2A does not begin with a methionine whereas the ORF codes for a methionine at position one. In addition the ORF corresponds to a polynucleotide sequence of 1,965 nucleic acids, which codes for a protein of 655 amino acids not 663 amino acids (as shown in Figure 2A of the provisional application). Therefore, it is apparent to me that

the amino acid sequence shown in Figure 2A is an obvious error and should have been the 655 amino acid sequence that corresponds to the ORF described at pages 21-22 of the provisional application, which as discussed above corresponds to SEQ ID NO:1 in European Patent No. EP 1 054 894.

6. In summary, it is my technical and professional expert opinion that the amino acid sequence of SEQ ID NO:1 in European Patent No. EP 1 054 894 can unequivocally be derived from US Provisional Patent Application Serial No. 60/073,763. In addition, it is also my opinion that the 663 deduced amino acid presented in Figure 2A of US Provisional Patent Application Serial No. 60/073,763 was an obvious error with the correct sequence being the sequence corresponding to the ORF stated in that application.

Dr. Willard M. Freeman

9/12/08
Date